62. THE NEED FOR CREATION OF THE INTERNATIONAL CENTER IN NOVOSIBIRSK, RUSSIA FOR COMBATING INFECTIOUS DISEASES AND BIOTERRORISM THREAT IN ASIA

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Our State Research Center of Virology and Biotechnology VECTOR was established back in 1974 as an All-Union Scientific Research Institute of Molecular Biology [1]. Its task was to conduct basic and applied research on extremely pathogenic viral agents such as less-studied Marburg, Ebola, Lassa and other viruses related to potential BW agents in order to evaluate the potential threat posed by these agents and develop means of their diagnostics, prevention, and therapy. Maximum biological containment laboratory facilities, the most modern in Russia, were built as well as an engineering infrastructure and a set of scientific and supporting capabilities. The total area of existing buildings and facilities amounted to 250,000 square meters.

In 1989, VECTOR already employed over 4,000 staff, including more than 250 Ph.D.'s and Doctors of Sciences. At that time, VECTOR received practically all of its funding from the federal budget and just began to establish manufacturing activities.

Access to workplaces by and communication with foreign scientists were practically impossible. The same situation was with the participation of VECTOR scientists in the international conferences and publication of scientific papers.

In 1989, it became obvious that VECTOR should undergo restructuring to try to adapt itself to changing economic conditions that ultimately resulted in a significant cutback of federal budget funding. A program of VECTOR's long-range development was prepared that focused on conducting much more public health and veterinary medicine oriented research on infectious diseases and development of diagnostic tests, vaccines and antivirals as well as a set up of manufacture of diagnostic, therapeutic and prophylactic products.

In 1993, VECTOR became a Russian State Research Center and started to receive federal budget funding to support its R&D activities through civilian government programs. The development of pharmaceutical manufacturing activities was supported by government investments and credits, which allowed us to renovate and upgrade several facilities and purchase some equipment necessary for drug production.

Currently VECTOR is a scientific center consisting of six scientific research institutes and three daughter companies manufacturing a broad range of products. However, we should admit that the restructuring process was difficult and troublesome since the economic situation in Russia, especially the fluctuations of the ruble in 1992-1996 and 1998, produced a detrimental impact on science and production in Russia. The number of employees at VECTOR decreased more than two times: currently we employ at VECTOR 1887 staff. Of these, 1212 are those directly involved in or support of scientific research and 675 are employed in the manufacturing area. Over 50 VECTOR researchers left VECTOR for abroad during 1993-1998 and are doing a successful job at prestigious scientific research centers in the United States, Canada, France, Germany, Italy, Australia, New Zealand and Sweden.

However, VECTOR did manage to maintain most of its key scientific personnel and establish sustainable manufacturing activities. During the recent years, VECTOR's income pattern has changed dramatically. If in 1990 78% of funds came from the federal budget, in 2000 77% of the total income was accounted for by the sales of products.

It should be specially mentioned about the role of international assistance provided to VECTOR in its reorientation towards public health and agriculture-oriented programs.

In 1992, an International Science and Technology Center (ISTC) was established as a nonproliferation-targeted program for the Newly Independent States. The similar goal was set for the US Civilian Research and Development Foundation (CRDF) that was established by the U.S. National Science Foundation in 1995, and for the Newly Independent States Industrial Partnering Program (NIS-IPP, currently more known as Initiatives for Proliferation Prevention) that is being carried out through the US Department of Energy with the involvement of the United States Industry Coalition (USIC).

In 1995, the first projects with these agencies were launched. During 1995-2000, we completed 29 projects, including 15 ISTC projects. Today, we have 26 active projects, including 23 ISTC-funded projects. In 1998, these projects began to play a significant role in VECTOR's budget whereas the contribution they made amounted to 30% of the Russian federal budget funding of VECTOR. As of today, the size of funding under the project agreements concluded is US$ 9,910,936, including US$ 9,610,936 provided under the ISTC-funded projects.

We can hardly overestimate the importance of ISTC for our Center because ISTC has made a tremendous contribution to VECTOR and VECTOR scientists' integration into the world's scientific community. Grant funding allows us to receive our foreign colleagues and, in turn travel ourselves to get acquainted with foreign laboratories. VECTOR employees have attended dozens of international conferences and workshops using ISTC support. Hundreds of our scientists have visited their foreign counterparts on site. It made it possible to create an atmosphere of openness and transparency at VECTOR, which is critical to science and scientists. Thanks to support provided for our scientific staff, we have been able to renew and maintain our relationships with NIS scientists and scientists from other regions in Russia.

Our employees attend all the refresher courses: English language, patent, R&D commercialization program; GLP, GCP and GMP training programs. It helped us realize that without constant implementing international quality standards in science and production we could hardly hope for our R&D products' being competitive on the world market.

Thanks to grant funding, our scientists are able to conduct research using up-to-date equipment and supplies as well as the latest techniques to gain world-class results.

Thanks to grant funding, technology of hepatitis A vaccine production, that of production of a diagnostic kit for opisthorchiasis and other infections have been developed. Technology of oral measles vaccine production and that of influenza vaccine are in the final developmental stages. These developments, besides many others, allowed us to establish manufacturing activities at our daughter enterprises that have become totally self-sustainable.

There were opinions in US press that grant-funded research is poorly coordinated and chaotic. We cannot agree with it. During the most recent years, the coordination of projects has improved dramatically when the so-called *Partner Projects* appeared. Currently at ISTC, Partner Projects have been initiated with US DHHS (BTEP/FETP), USDA (ARS USDA), DOD (DTRA, DARPA). With these projects, the Partner and the Russian institute jointly formulate high-priority goals and tasks for which the projects are being tailored individually.

For instance, with BTEP it is the study of infections representing serious public health problems such as HIV/AIDS, multi-drug-resistant tuberculosis, hepatitis, measles, etc. And these investigations are being started with establishing the international ethical standards at VECTOR in accordance with international GCP regulations. Two very perspective projects will be started soon in the field of development of fast and very sensitive PCR-microchip detection of dangerous pathogen genomes in blood and other biological samples. The variola virus is being studied now in collaboration with U.S.scientists also because of this BTEP

program. The study of the latter infection is of special importance to current efforts to encounter the bioterrorism threat.

Very focused are also the efforts that are being planned and implemented under the U.S.A. Cooperative Threat Reduction (CTR) program that relate to upgrade the physical security and biosafety systems at the maximum biocontainment facilities at VECTOR up to the highest modern standards. Serious efforts are being taken to bring laboratory work, involving research animals, and pharmaceutical manufacture at VECTOR's daughter enterprises up to the GLP and GMP standards, respectively.

A few papers were published mentioning about the criticisms concerning the possible alleged use of US Government funds by Russian institutes for whatever prohibited purposes. These concerns have been voiced in the study prepared by the US General Accounting Office during the revision of five-year work of different U.S.government agencies funding of Russian biological centers [2], and in the study conducted by the Henry L. Stimson Center [3], and some others. In spite of the lack of evidentiary support of these statements, we should admit that it could change the situation in principle if the recipient institution working with the most dangerous pathogens was operating on an international regimen ensuring confidence and transparency. For several years already, we have been discussing this problem with representatives of the US State Department, US DHHS and Russian authorities. Now we are in the process of finalizing an ISTC proposal, "Development of Concept of an International Center for the Study of Emerging and Re-emerging Infectious Diseases", with our US collaborators [12].

By an *International Center* we mean an international organization established by an intergovernmental agreement, similar to those of ISTC (website www.istc.ru) or the Joint Institute for Nuclear Research in Dubna (see website http://www.jinr.ru), CERN in Switzerland (website http://www.cern.ch/) or International Center for Genetic Engineering and Biotechnology in Trieste, Italy (website http://www.icgeb.trieste.it/). Nonproliferation and threat reduction goals can only be achieved through transparency and confidence building when the *International Center* is established and operated with access to the program and results obtained, and with free access to financial information and to all facilities and all staff of the *Center*. Continuous involvement of foreign scientists in work at this *Center* would be a powerful instrument of confidence building. It is critical, therefore, that all high containment capabilities and necessary supporting facilities be incorporated into the *Center* to alleviate concerns over possible prohibited activity.

Though the process of establishing the *International Center* is complex and may take several years to complete, the proposed arrangement would provide for a long-term strategic collaboration, which is far less subject to political or economic conjuncture fluctuations in Member States. International efforts would accelerate both the study of dangerous pathogens and the development of state-of the-art public health products for diagnosis, prophylaxis and therapy.

The vital need to establish an international regimen to support research on pathogenic microorganisms is driven not only by political considerations. To date, both policy makers and scientists came to understand the global threat posed by infectious diseases to the humankind [4-8]. Nature has been leading a biological war against us that we can hardly win but we can work to ensure the safety of the humankind but only by global efforts of the countries worldwide. During the past 20 years, 30 new infectious diseases have emerged, e.g. HIV, Marburg, Ebola viruses, legionnaires' disease, drug-resistant TB forms, and many others. Death rates as a result of infectious diseases amount to 30% of the total fatality rates worldwide and these figures have been growing during the recent years [7]. It also should be mentioned that the situation with infectious diseases in Russia is not improving during the

last ten years ([8], see also Table 1). Tuberculosis increase is becoming a real threat to the nation's health (Fig.1), and, especially, its drug-resistant forms. It is an exponential increase of HIV cases (Fig.1), which is becoming now a real threat to the young people in Russia. There was a dramatic outbreak of diphtheria in the middle of 90's which seems to be caused by sharp decrease of revaccination among adults; this outbreak was managed only by unprecedently wide revaccination campaign on the state level for all the population. The big increase of measles cases (Fig.3) was caused by shortage of money for vaccines and was managed by a wide revaccination of teenagers. Mumps incidence (Fig.3) began to decrease only two years ago because of the start of mumps revaccination program. It is a constant growth in parenteral hepatitis B and C, mainly because of intravenous drug usage (Fig.4), but also because of mistakes in blood testing. These non-precedent outbreaks are needed to be thoroughly studied, for further usage of this experience for elaboration and maintenance of the most effective vaccination strategies for these infections.

Infections mind no borders nor they distinguish between the rich and the poor [9]. Therefore, global monitoring over outbreaks of infectious diseases is required. To remind you, a concept of international collaboration in the area of pathogens research was developed in 1997 by an expert group of the US National Academy of Sciences (NAS) under the leadership of Prof. Joshua Lederberg and Dr. John Steinbrunner [10]. Unfortunately, at that time it did not receive financial support. In general, the need for international collaboration to combat infectious disease is beyond all doubt and supported by policy makers and scientists. More detailed proposals are now being considered by WHO known as the Strategic Alliance against Infectious Disease Program.

The geographical location of the Center – near the geographical center of Russia - is very suitable for the most effective collection of natural viral and bacterial strains and diagnostic procedures for the study of specimens from Asian Russia, Central Asia FSU republics, Mongolia and other neighbor countries, if needed, because Novosibirsk is the largest in the area transportation hub. This location of the proposed *International Center* would also allow us to join international efforts to control and deter potential bioterrorists.

The establishment of the International Center for Emerging Infectious Diseases (ICERID) here, in Vector would, in our opinion, be a qualitatively new step towards implementing agreements on the cooperative threat reduction and this approach then could be applied at other institutions.

The unique features of Vector facilities, staff and achievements are presented in the numerous publications and in the web [1, 11] but it will be helpful to present here some details.

The research and technical staff of the VECTOR (1,200) is represented by highly qualified personnel specializing in the field of genetic engineering, molecular biology, virology, theoretical virology, immunology, epidemiology, ecology with an extensive experience in highly dangerous viruses research and in production of diagnostic and prophylactic preparations for public health and veterinary needs. 157 of 340 researchers have now Candidate (Ph.D. equivalent) and Doctor of Science's degrees.

The Collection of Cultures of Microorganisms available in the Center comprises over 10,000 deposit entries: various viral strains, including the national collection of variola virus strains and strains of viral BSL-4 pathogens. The Collection received an international recognition in 1995 when it was affiliated with the European Culture Collection Organization (ECCO).

VECTOR houses one of the two WHO Collaborating Centers (WHO Collaborating Center for orthopoxvirus diagnosis and repository for variola virus strains and DNA), supplied with all required conditions for work with human highly pathogenic viruses,

including variola virus. One of the terms of reference of this WHO Collaborating Center is to preserve and study the Russian collection of variola virus isolates, to develop modern diagnostic kits, improved vaccines and new therapeutic means. The other WHO Collaborating Center for Smallpox and Other Poxvirus Infections is located at CDC in Atlanta, USA. Research collaboration that is established between these two Centers is promising in terms of basic science and, which is of equal importance, in terms of confidence building.

VECTOR has a Breeding and Holding Facility for laboratory animals, including primates that are used in trials on therapeutic and diagnostic preparations being developed at VECTOR. Facilities for the performance of preclinical and clinical trials of new medicinal preparations are available at VECTOR. It is important that Center has a long-term experience in ecology research: one of the divisions of the Center, actively participated in studying the environmental situation in different cities of Kuzbass (Kemerovo Region) coal mines region and developed recommendations for diminishing pollution there. This department continues this study now using for this purpose modern and unique tailor-made equipment and modern mathematical methods.

VECTOR houses a Chair of Basic Medicine of the Novosibirsk State University which makes it possible to involve students and undergraduates of the University in research work of the International Center.

At VECTOR we have a Novosibirsk Regional Center for the Prophylaxis and Prevention against AIDS located on the territory of a specialized clinical isolation department with Biosafety Level 3; at our base, we also house a children's TB hospital.

As objects for research to be carried out at the proposed *International Center* could be arboviruses, including tick-borne encephalitis virus which is endemic in Russia; HFRS virus, Omsk hemorrhagic fever virus – both also endemic in Siberia; filoviruses: Marburg and Ebola; orthopoxviruses: smallpox virus, monkeypox, and cowpox viruses; viruses causing hepatitis A, B, C and HIV-1; measles, mumps, rabdoviruses, influenza viruses, etc. This list of viruses could be extended by bacteria and parasites, and already includes tuberculosis, which is increasing sharply now in Russia, and opistorchiasis – human parasitic disease, which affect liver and is endemic in Siberia too. It also makes sense to address another viruses causing zoonotic and anthropozoonotic diseases critical to public health and veterinary in the region. As a result of this research, the proposed *International Center* can have as one of its strategic scientific goals such as making prognosis, based on the data of global monitoring, of what new infections might emerge in the future. It should be noticed that the most of these infectious agents are considered to be possible bioterrorism agents, and therefore the proposed ICERID could develop the preventive research in anti-bioterrorism direction.

Research areas should cover fundamental aspects of genetics, physiology, and biochemistry of pathogens; pathogenesis studies, including those on human immune response to an infectious disease; development of diagnostic methods; development of drugs and vaccines; epidemiological studies, including the investigation of environmental factors and their effect on rodents and insects; the effect of human behavior and demography, etc.

It is also important to carefully address the issue of enrolling the staff in various training and exchange programs, with invitation for research work at the Centers of foreign scientists and training of our scientists abroad. It is critical to consider the issue of an appropriate handling of microorganisms.

The special attention would be paid to the investigation of the unusual outbreaks of infectious diseases in the region (Asian part of Russia, Central Asian republics – members of C.I.S., possibly – another countries of the region). This investigation may be conducted using

molecular epidemiology approach, which allows to determine the sero- and genotypes of infectious agents, the source of primary infection and even to help distinguishing whether it is intentional or natural outbreak. It was an outstanding example of such an investigation in USA two years ago, when the intentional HIV infection of former lover by physician through injection had been proved by molecular epidemiology methods, and this physician had been put into prison. Such investigations may be made on regular basis for a wide list of pathogens. This type of research would be extremely useful both for monitoring of the evolution and spread of infectious agents and for the investigation of possible bioterrorism cases.

Of course, these are only some baselines for possible scientific program that will be refined and finalized by the Scientific Councils of proposed Center if a positive decision is made that the proposed *International Center* be finally established. In conclusion we would like to address the advantages that come with the creation of the *International Center*:

1. The proposed *International Center* will be able to provide the modern fast diagnostics and monitoring of infectious disease agents in the vast territory of Northern Asia which would be extremely helpful for prognosis of evolution and possible emerging of infectious diseases which are endemic here.
2. The Center will help the public health institutions in the North and Central Asian Countries in investigation of infectious diseases transmission ways and in development of prevention measures and modern diagnostics introduction.
3. International efforts will provide for the highest level of knowledge and accelerate both the study of dangerous pathogens and the development of state-of-the-art public health products for diagnosis, prophylaxis and therapy.
4. The proposed *International Center* in Vector could provide a long-term strategic collaboration, which is far less subject to political or economic conjuncture fluctuations in Member States.
5. The creation of the proposed *International Center* will make it possible to join our efforts to gain knowledge that is essential to control potential bioterrorists.

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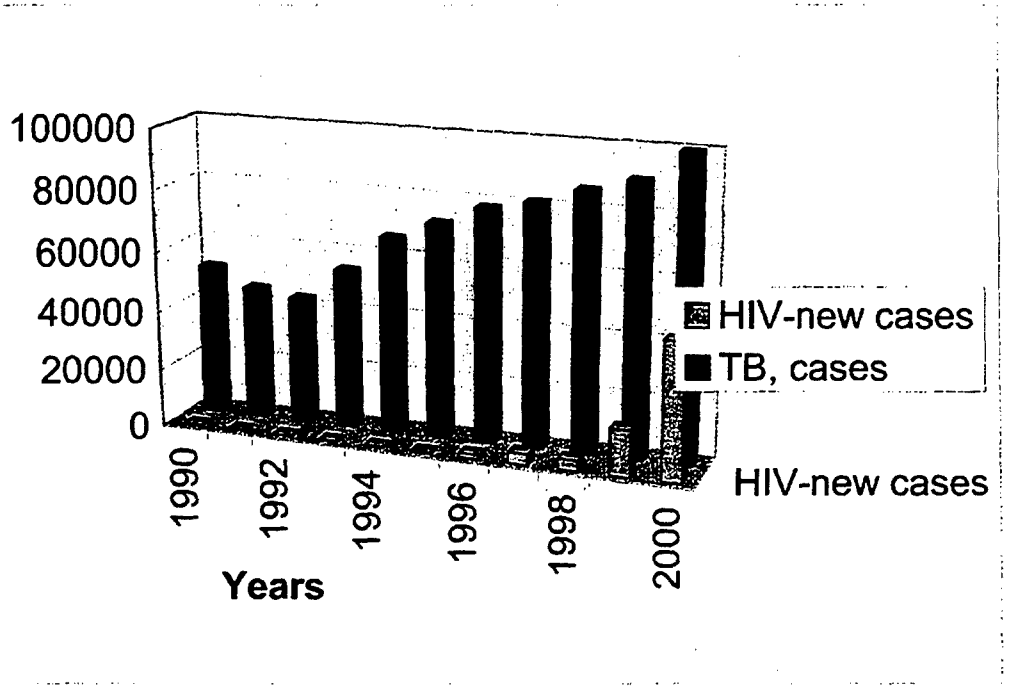

Figure 1. The Tuberculosis and HIV-1 morbidity data in Russian Federation in 1990-2000 (absolute amounts of cases).

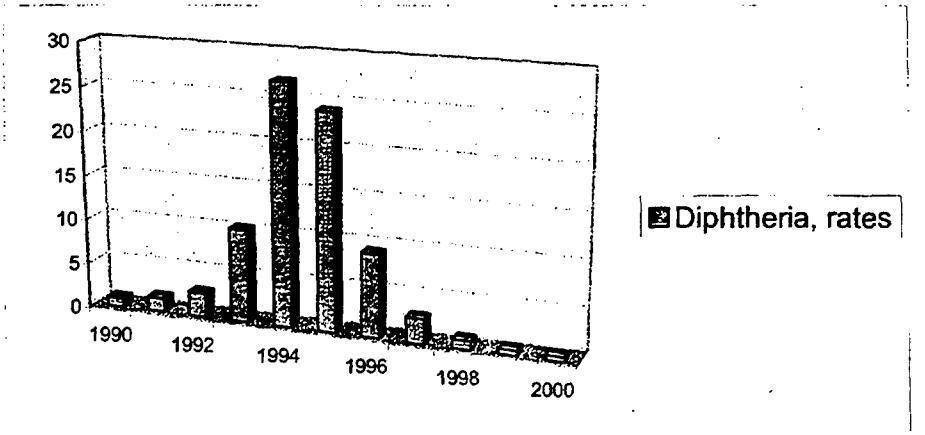

Figure 2. The Diphtheria Morbidity in Russian Federation during 1990-2000, cases per 100,000 (rates)

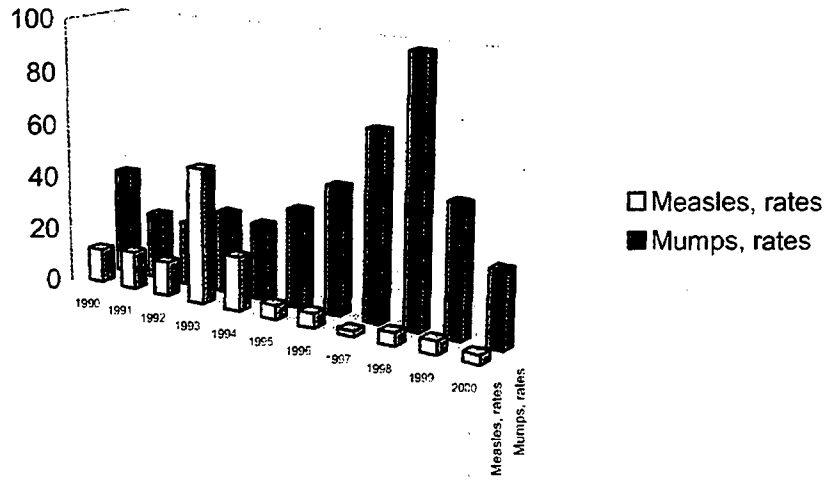

Figure 3. The Measles and Mumps Morbidity data in Russia in 1990-2000, cases per 100,000 rates).

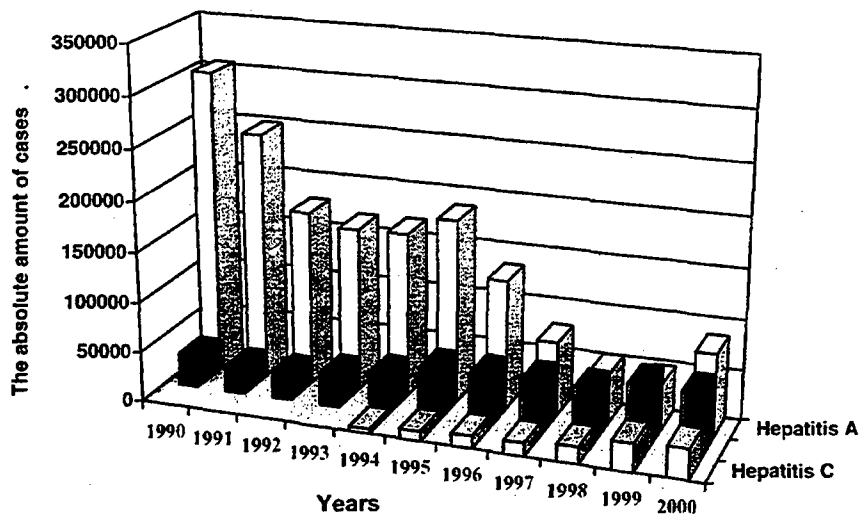

Figure 4. The Acute Viral Hepatitis Morbidity Data in Russia, 1990-2000, cases per 100,000.

Table 1 Selected reportable Diseases, Russian Federation, 1990-2000

Years **Diseases, per 100,000 if not shown other**	**1990**	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**
Diphtheria	0.98	1.53	2.65	10.25	26.9	24.1	9.2	2.76	0.98	0.6	0.53
TB, cases	51,000	45,000	43,000	54,000	66,000	72,000	78,000	81,000	86,000	90,044	99,932
TB-all	34.2	34	35.8	42.9	48	57.9	67.5	74	76	n.a.	n.a.
TB-MOH	34.3	30.5	29.4	36.5	45.1	48.7	52.8	55.1	58.5	61.14	68,47
TB-mortality	7.9	8.1	9.3	12.6	14.6	15.4	17	16.7	n.a.	n.a.	n.a.
Syphilis	5.4	7.3	12.6	32.3	82.3	172.1	254.2	266.8	226.1	179.3	157.3
Shigella	130.4	146.6	127.3	102.4	149.9	184.2	82	57.1	78	148.4	123.5
Hepatitis A	204.3	165.5	117.9	109.3	111.2	122.6	86.9	50.1	33.8	30.6	56.49
Hepatitis B	21.9	17.9	18.2	22.2	27	35.2	35.8	36.5	35.8	43.3	42.14
Hepatitis C	nd	nd	nd	nd	3.2	6.8	8.4	9.1	11.6	19.3	20.73
Measles	12.4	13.8	12.6	50.1	20	5.2	5.4	2	4.7	5.0	3.38
Mumps	39.2	24.6	23.6	30.1	28.1	36.1	47	69.2	97.8	48.2	27.91
Rubella	192.6	141	na	127	245.7	186.2	115.5	121.1	304	407	310.3
TBEV	3.7	3.5	4.3	5.3	4	4	6.5	4.4	5	6.7	4.03
Influenza	3,719	4,823	6,097	3, 721	2,339	3,870	2,450	5,060	2,516	4,059	5,220
HIV-new cases	95	66	72	99	146	169	1,433	3,853	3,709	15,908	46,438
HIV, rates, new cases	0.06	0.04	0.05	0.07	0.1	0.11	0.97	2.6	2.5	10.84	31.82
Omsk hemorrhagic fever, cases	29	41	7	19	11	5	2	na	7	n.a.	n.a.

Rates /100,000 population